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Autonomic dysfunction in isolated rapid eye movement sleep without atonia

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HIGHLIGHTS

- Isolated REM sleep without atonia (RSWA) is of unclear clinical significance.
- We demonstrate a significant reduction in several parameters of HRV in isolated RSWA.
- This is the first report of possible autonomic dysfunction in isolated RSWA.

ABSTRACT

Objectives: Autonomic dysfunction has been demonstrated in patients with rapid eye movement sleep behavior disorder utilizing heart rate variability parameters. We hypothesized that isolated rapid eye movement sleep without atonia is similarly associated with autonomic dysfunction as demonstrated by a reduction in heart rate variability.

Methods: An evaluation of 120 records demonstrating rapid eye movement sleep without atonia during polysomnography was performed. Many ($n = 99$) were discarded owing to factors potentially affecting heart rate variability. The remaining 21 records were matched with 21 records of patients demonstrating normal REM atonia, and subjected to electrocardiogram analysis. The parameters measured included R to R interval (RR) length, RR standard deviation, heart rate variability power, and very low frequency, low frequency, and high frequency bands.

Results: Autonomic dysfunction was seen in patients with isolated rapid eye movement sleep without atonia as denoted by a reduction in heart rate variability compared to those with normal REM atonia. Significant differences between the groups were demonstrated in RR standard deviation (mean difference = 0.1502 ± 0.317, 95% confidence interval [95% *CI*]=0.006, 0.295, $p = 0.042$), heart rate variability power (mean difference = 0.3005 ± 0.635, 95% *CI* = 0.011, 0.589, $p = 0.042$), and the low frequency band (mean difference = 0.3166 ± 0.616 ms^2, 95% *CI* = 0.036, 0.597, $p = 0.029$), and a borderline significant reduction in the high frequency band (mean difference = 0.3121 ± 0.686 ms^2, 95% *CI* = 0.000, 0.624, $p = 0.050$).

Conclusions: Our data confirms the hypothesis that heart rate variability is reduced in patients with isolated rapid eye movement sleep without atonia. The values obtained are consistent with previous findings in rapid eye movement behavior sleep disorder patients.

Significance: This is the first report of autonomic dysfunction in isolated rapid eye movement sleep without atonia, revealing the need for further evaluation of the clinical significance and potential implications of this finding.

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1. Introduction

Formally characterized in 1986 (Schenck et al., 1986), rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia consisting of REM sleep without atonia (RSWA) in combination with a history of recurrent nocturnal dream enactment behavior (DEB) (Olson et al., 2000; Schenck and Mahowald, 2002; Arnulf, 2012). During normal REM sleep, there is active inhibition of electromyogram (EMG) activity leading to complete or near complete atonia; RSWA represents the polysomnogram (PSG) finding of abnormally increased EMG tone based on American Academy of Sleep Medicine scoring manual standards (Berry et al., 2012). Multiple neurotransmitter systems are responsible for regulating postural muscle tone during REM sleep (Boeve et al., 2007; Luppi et al., 2012); specifically, inputs from REM atonia circuits activate glycinergic and GABAergic premotor neurons that inhibit motor neurons (Ramaligam et al., 2013). The perilocus coeruleus, located in the rostral pons, exerts an excitatory influence on the medullary reticular formation through the lateral tegmentoreticular tract. These neuronal groups then hyperpolarize the spinal motor neuron postsynaptic membranes through the ventrolateral reticulospinal tract. In RBD, the brainstem mechanisms generating the muscle atonia normally seen in REM sleep may be disrupted (Kryger and Avidan, 2010).

According to the International Classification of Sleep Disorders, 2nd edition (ICSD-2), the clinical diagnosis of RBD requires: the presence of RSWA on overnight PSG and either sleep-related injurious, potentially injurious, or disruptive behaviors by history, and/or abnormal REM sleep behavior documented during PSG monitoring. Additionally, there must be an absence of epileptiform activity on electroencephalography during REM sleep, and the sleep disorder cannot be better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder (American Academy of Sleep Medicine, 2005).

There have been numerous recent reports suggesting that autonomic function is impaired in RBD. Patients with idiopathic RBD have a higher frequency of constipation, erectile dysfunction, and orthostatic blood pressure changes compared with controls (Postuma et al., 2006, 2009). Studies of RBD patients using cardiac metaiodobenzylguanidine scintigraphy have demonstrated postganglionic degeneration of cardiac sympathetic neurons (Miyamoto et al., 2006), and that the presence of RBD in Parkinson's disease may reflect profound synuclein pathology (Nomura et al., 2010). Prior studies have demonstrated abnormal beat-to-beat variability in idiopathic RBD (Ferini-Strambi et al., 1996), as well as an absence of REM-related cardiac and respiratory responses (Lanfranchi et al., 2007). The pattern of autonomic dysfunction in idiopathic RBD is similar to that reported in idiopathic Parkinson's disease (Haapaniemi et al., 2001). The pathophysiological mechanisms of RBD are not fully understood, but neuropathological and imaging studies performed in RBD patients have demonstrated abnormalities in several brainstem areas (Gagnon et al., 2006), and it is possible that brainstem structures contributing to the central autonomic network are also affected by this neuronal damage (Lanfranchi et al., 2007).

In 2010, Postuma et al. demonstrated that RBD is associated with autonomic dysfunction as measured by a reduction in heart rate variability (HRV), irrespective of whether the patient develops synucleopathy (Postuma et al., 2010). In their study, an analysis of HRV was performed on the electrocardiogram (ECG) portion of 5-min epochs representing continuous wake for both RBD subjects and controls (Postuma et al., 2010). Our study was designed to test the hypothesis that isolated RSWA (without DEB, from the history and video recording of PSG) is associated with autonomic dysfunction as measured by HRV.

2. Methods

This study was approved by the institutional review board at Weill Cornell Medical College. All PSG records and clinical data from adult patients (ages 18–80) diagnosed with RSWA and recorded at the Weill Cornell Center for Sleep Medicine from July 2010 to June 2013 were analyzed. All patients underwent PSG testing as part of the clinical evaluation of sleep disorders including snoring, obstructive sleep apnea, insomnia, hypersomnia. The scoring of RSWA was performed by registered technologists, according to the AASM scoring manual guidelines (Berry et al., 2012), which includes either sustained muscle activity (tonic activity) of the chin EMG or excessive transient muscle activity (phasic activity) of the chin or limb EMG during REM sleep. The EMG technical specifications were as follows: sampling rate of 200 Hz, low frequency filter of 10 Hz, high frequency filter of 100 Hz, maximum electrode impedance of 5 KΩ, and digital resolution was 16 bits per sample.

For tonic activity, an epoch of REM sleep with at least 50% of the duration of the epoch having chin EMG amplitude greater than the minimum amplitude demonstrated in NREM sleep was considered RSWA. For phasic activity, a 30-s epoch of REM sleep was divided into 10 sequential, 3-s mini-epochs, and RSWA was scored if at least 5 (50%) of the mini-epochs contained bursts of transient muscle activity in the chin or limb EMG. Excessive transient muscle activity bursts were defined as 0.1–5.0 s in duration and at least 4 times as high in amplitude as the background EMG activity (Berry et al., 2012).

A total of 120 records demonstrated RSWA, and patients with potential confounding factors that could affect HRV analyses were excluded ($n = 99$) based on the following criteria: clinical diagnosis of RBD with a history of DEB or a history of conditions associated with RBD (synucleopathies such as Parkinson's disease), respiratory disturbance index (RDI)>15/h (in order to exclude pseudo-RBD) (Iranzo and Santamaria, 2005) and to be consistent with other work (Montplaisir et al., 2010; Postuma et al., 2010), seizure activity on PSG, use of medications associated with RSWA (e.g. antidepressants) (Hoque and Chesson, 2010), diagnosis of narcolepsy (Dauvilliers et al., 2012), alcohol intake (night of the study and/or a history of abuse) (Nardone et al., 2013), history of cardiac arrhythmias, and use of medications affecting the heart rate (particularly beta blockers, calcium channel blockers, and amphetamines) (See Fig. 1).

Twenty-one patients remained for analysis, and were age- and sex-matched with 21 patients taken from a pool of polysomographic studies during the same time frame, and meeting the same exclusionary criteria, save for the fact that they exhibited normal REM atonia. These polysomnograms were performed as part of an evaluation of the various sleep disorders mentioned previously.

Demographic data and multiple facets of PSG data were compiled for both groups. The determination of HRV was based on 5-min epochs of ECG data during continuous wakefulness taken from full-night PSGs, consistent with previous studies (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Postuma et al., 2010). The data were then analyzed in the time- and frequency-domains using the SuperECG Package software (Mortara Instrument, Inc., Milwaukee, WI) (Penn State University College of Medicine, 2008; Liao et al., 2010; Rodriguez-Colon et al., 2010; He et al., 2011). Time-domain variables included mean RR interval (conventionally labeled "NN" to indicate "normal beats") and standard deviation of the RR intervals (conventionally labeled "SDNN") (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Frequency-domain variables included components of RR variability quantified by an autoregressive decomposition algorithm to compute spectral peak powers

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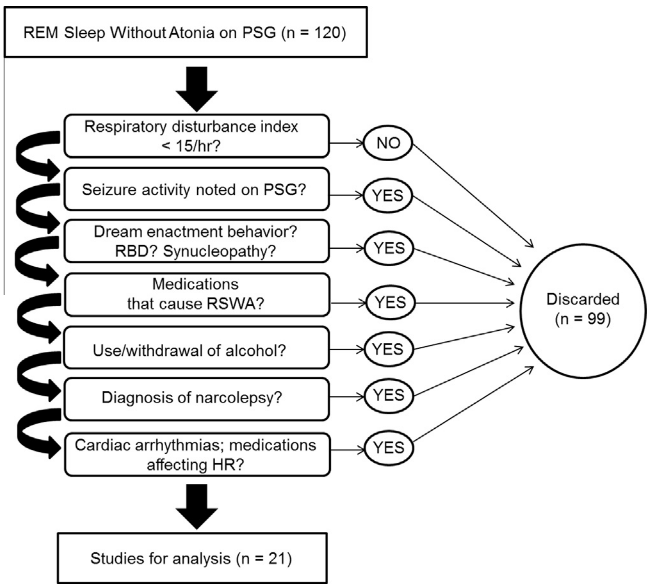

Fig. 1. Flow chart of studies selected for analysis.

and their central frequencies, which are then classified into very low frequency (VLF; <0.04 Hz), low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz) bands (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The HRV data was then complied and further analyzed using SPSS 21 software (IBM, Corp., Armonk, New York). All variables were positively skewed; therefore, log transformations were performed to normalize the data. Paired-samples *t*-tests were conducted to test for significant differences between the matched pairs on all variables tested. Samples were compared to their matched pairs to reduce the influence of age and gender on EMG activity in REM sleep.

3. Results

The RSWA group consisted of 21 patients, 18 (86%) of which were men; the REM atonia group consisted of 21 patients, matched as pairs. The demographic and baseline PSG data of the two groups are shown in Table 1 and the reasons for polysomnographic testing along with the final diagnoses of all 42 patients are shown in Table 2. There was no statistically significant difference in sleep architecture between groups; however, the groups exhibited significant differences in periodic limb movements in sleep (PLMS) and PLMS arousal indices, both of which were higher in the RSWA group.

Reduced HRV was found in the RSWA group compared to the REM atonia group (Table 3) in both time and frequency domain variables. With the alpha set to $p < 0.05$, there were significant reductions in RR standard deviation (mean difference = 0.1502 ± 0.317 ms, 95% confidence interval [95% *CI*]=0.006, 0.295, $p = 0.042$), heart rate variability total power (mean difference = 0.3005 ± 0.635 ms^2, 95% *CI* = 0.011, 0.589, $p = 0.042$) and the low frequency band (mean difference = 0.3166 ± 0.616 ms^2, 95% *CI* = 0.036, 0.597, $p = 0.029$) and a borderline significant reduction in the high frequency band (mean difference = 0.3121 ± 0.686 ms^2, 95% *CI* = 0.000, 0.624, $p = 0.050$). Of these reduced HRV parameters, no statistically significant correlations were found with PLMS or PLMS arousal indices at $p < 0.05$ for either group.

4. Discussion

This study is the first to demonstrate reduced heart rate variability in patients with isolated RSWA as compared to those with normal REM atonia. Consistent with our hypothesis, the statistically significant differences in heart rate variability in the RSWA group may reflect underlying autonomic dysfunction. The values obtained from these analyses have been found to correlate with certain autonomic parameters: SDNN likely represents the overall index of beat-to-beat variability, and HRV total power is similarly a global measure of variability (Postuma et al., 2010), while the HF band likely represents the respiration-driven vagal modulation of sinus rhythm (Eckberg, 2000). Disagreement exists with respect to the LF band: some view it as a quantitative marker for sympathetic modulations, and others view it as reflecting both sympathetic and vagal activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Eckberg, 2000), or the baroreflex responsiveness to beat-to-beat variations in blood pressure (Sleight et al., 1995). Physiological interpretation of the VLF band still warrants further elucidation (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), but it has been demonstrated to be related to sympathetic activity (Ergun et al., 2008). Recent reports indicate that there exists a reduction in VLF during wakefulness in idiopathic RBD patients (Sorensen et al., 2013), thus indicating that there may be an attenuation of sympathetic nervous system activity in these patients.

It is important to note that while there does not yet exist normative data regarding HRV (Nunan et al., 2010), the parameters

Table 1
Baseline demographic and polysomnogram characteristics of all patients.

	REM atonia (*n* = 21)	RSWA (*n* = 21)	*P* value (two-tailed)
Age (years)	36.9 ± 12.3	36.6 ± 12.4	0.249
Body mass index (kg/m^2)	25.7 ± 3.8	27.5 ± 5.6	0.242
Sex	18 M (86%)	18 M (86%)	N/A
Epworth sleepiness scale	6.6 ± 4.2	8.3 ± 5.3	0.192
Total sleep time (min)	375.5 ± 63.6	393.6 ± 68.3	0.299
% NREM 1	10.1 ± 6.0	11.6 ± 5.6	0.388
% NREM 2	61.0 ± 10.0	59.2 ± 9.4	0.562
% NREM 3	10.1 ± 9.5	8.3 ± 7.9	0.447
% REM	18.8 ± 5.9	20.9 ± 5.6	0.147
Sleep efficiency (%)	78.4 ± 11.1	83.4 ± 6.9	0.060
WASO (min)	74.8 ± 62.4	60.9 ± 31.1	0.348
RDI (events/hr)	5.0 ± 2.6	4.2 ± 3.2	0.360
PLMS index (events/hr)*	0.6 ± 1.6	8.0 ± 14.6	0.034
PLMS arousal index (events/h)*	0.005 ± 0.02	0.2 ± 0.4	0.038
Total arousals (events/h)	6.8 ± 3.4	7.2 ± 3.5	0.691

WASO wake after sleep onset, *RDI* respiratory disturbance index, *PLMS* period limb movements in sleep.
* $p < 0.05$.

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Table 2
Reasons for polysomnographic testing and final diagnoses of all patients.

	REM atonia ($n = 21$)		RSWA ($n = 21$)	
	Reason for PSG	Final diagnosis	Reason for PSG	Final diagnosis
Primary snoring	38% (8)	67% (14)	33% (7)	43% (9)
OSA; SDB	24% (5)	33% (7)	24% (5)	29% (6)
Insomnia	14% (3)	0% (0)	14% (3)	0% (0)
Excessive sleepiness; Hypersomnia; fatigue	24% (5)	0% (0)	29% (6)	19% (4)
RLS; PLMD	0% (0)	0% (0)	0% (0)	9% (2)

PSG polysomnogram, *OSA* obstructive sleep apnea, *SDB* sleep disordered breathing, *RLS* restless legs syndrome, *PLMD* period limb movement disorder.

Table 3
Analysis of paired differences between groups for measures of heart rate variability (log-transformed).

Heart rate parameter	Mean value REM atonia; RWSA	Paired differences mean	95% Confidence interval lower	95% Confidence interval upper	*P* value (two-tailed)
NN interval length (ms)	2.99 ± 0.06 2.96 ± 0.07	0.0263 ± 0.102	−0.020	0.073	0.252
SDNN (ms)*	1.90 ± 0.26 1.75 ± 0.27	0.1502 ± 0.317	0.006	0.295	0.042
Heart rate variability power (ms^2)*	3.81 ± 0.52 3.51 ± 0.55	0.3005 ± 0.635	0.011	0.589	0.042
Very low frequency band (ms^2)	3.29 ± 0.55 3.04 ± 0.55	0.2575 ± 0.746	−0.082	0.597	0.129
Low frequency band (ms^2)*	3.24 ± 0.53 2.92 ± 0.55	0.3166 ± 0.616	0.036	0.597	0.029
High frequency band (ms^2)	3.12 ± 0.65 2.80 ± 0.61	0.3121 ± 0.686	−0.000	0.624	0.050

NN Interval Length RR Interval Length, *SDNN* Standard Deviation of RR Interval Length.
* $p < 0.05$.

of SDNN and HRV total power were found to be significantly reduced in the RSWA group in our study, which is in agreement with the findings in RBD patients by Postuma (Postuma et al., 2010). Interestingly, both the LF and HF bands were reduced (albeit with borderline significance in the HF band) in the RSWA group, which implies that perhaps the abnormalities detected in RSWA are present throughout both components of the autonomic neuraxis. However, given that both VLF and LF bands are reduced in idiopathic RBD patients (Postuma et al., 2010; Sorensen et al., 2013), and of these, only the LF band was reduced in our RSWA patients, it could be hypothesized that the development of clinical RBD is concordant with a more profound decrease in sympathetic nervous system activity.

Some studies (Pagani et al., 1984, 1986; Malliani et al., 1991) have suggested that the ratio of LF to HF (LF/HF) could be used to quantify sympatho-vagal balance, but this concept has been challenged (Kingwell et al., 1994; Koh et al., 1994; Hopf et al., 1995; Eckberg, 1997; Billman, 2011). Given the controversial nature regarding its use (Billman, 2013), we chose to avoid this metric as part of our analysis.

With respect to baseline PSG data, the finding of significant differences in PLMS and PLMS arousal indices between groups is quite interesting, as PLMS are frequently observed in patients with RBD (Fantini et al., 2002; Sasai et al., 2011). It should be noted, however, that neither group exhibited an average PLMS index above the normal threshold of 15 h, per ICSD-2 criteria (American Academy of Sleep Medicine, 2005). The elevated PLMS index in the RSWA group may have elevated the PLMS arousal index, simply because there were more PLMS in this group. Additionally, the total arousal index was similar in both groups.

The limitations of our study include the retrospective nature of its design, the small sample size, and a lack of a clinical RBD group for further comparison. Additionally, the presence or lack of DEB was ascertained by review of clinical charts and patient-completed extensive sleep questionnaires (which did include specific questions regarding DEB). While these entities were carefully examined for any mention of what could potentially be construed as DEB, we cannot be certain that every case of DEB was screened out. Additionally, later development of DEB could not been ascertained during this study. Nonetheless, the screening process for DEB was similar between groups. Additionally, a recent longitudinal study demonstrated that HRV measurements are lower in advanced ages compared to younger ones, as demonstrated in cross-sectional analysis (Moles et al., 2013), and the RSWA patients in our study were, on average, younger than typical RBD patients; however, the fact that the groups were age-matched accounts for this potential limitation. It would be interesting to have both groups followed over time to assess the development of DEB in the RSWA group, as well as to detect a change in HRV in both groups. Finally, it should be noted that the two groups were not matched for physical activity levels, and while the body mass indices were not statistically different, it is possible that if the REM atonia group was more physically active this could potentially have skewed the results to favor increased HRV in these patients (Kaikkonen et al., 2014).

Rapid eye movement sleep without atonia, when seen not within the context of medication, significant sleep apnea, RBD, synucleopathy, or other neurologic disease, can be a potentially confusing entity for clinicians (Boeve, 2010). It is clear that in the presence of DEB, RSWA is a problem that requires further investigation by the clinician, but the question raised by this study is whether isolated RSWA is a clinically relevant finding. Postuma et al. postulated that autonomic dysfunction may be integrally related to the pathogenesis of RBD, rather than simply a finding of preclinical synucleopathy (Postuma et al., 2010); suggesting that perhaps isolated RSWA does, in fact, represent a preclinical form of RBD. Our data points towards autonomic changes in isolated RSWA that deserve further elucidation, and a recent editorial by Lam et al. corroborates this idea (Lam et al., 2013). Appropriately powered prospective studies will help elucidate this question.

Conflict of interest statement

Daniel A. Barone, MD, Matthew R. Ebben, PhD, Ashkan Samie, MD, Ana C. Krieger, MD, MPH does not have potential conflicts of interest to be disclosed.

David Mortara, PhD is the owner of Mortara Instrument Inc.

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